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REVIEW ARTICLE

Current developments in the management of post-operative nausea and vomiting

Evolución actual del tratamiento de las náuseas y los vómitos postoperatorios

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Abstract

Post-operative nausea and vomiting (PONV) is a common adverse event after surgery, with significant clinical and financial consequences. This article reviews the current evidence-based recommendations for its management, including key aspects in management: the evaluation of risk factors, both of the patient and related to anesthesia and the type of procedure, were review pharmacologic and non pharmacologic interventions such as rehydration, implementation of regional anesthesia techniques, avoidance of halogenated anesthestics and reduce opioid consumption in the perioperative period. The use of various pharmacological options stands out, including 5HT-3 receptor antagonists, neurokinin-1 receptor inhibitors, corticosteroids, antidopaminergics, antihistamines, dexmedetomidine, propofol, mirtazapine, and lidocaine. The most relevant drugs are detailed, highlighting their effectiveness and security profiles. In addition, combined strategies and multimodal therapies are explored. Non-pharmacological approaches such as acupuncture are examined, highlighting their pre-operative application and relevance in traditional medicine. Guidance is provided to address situations where prophylaxis fails to prevent PONV, highlighting the importance of drug combinations to improve the effectiveness of rescue treatment. The article concludes by noting the evolution toward multimodal approaches in the management of PONV, highlighting the diversity of available measures and the need for additional research to determine optimal strategies in specific clinical contexts.

Keywords: *Nausea. Vomiting. Pharmacology. Prophylaxis. Multimodal management.*

Resumen

La náusea y vómito postoperatorio (NVPO) constituye un evento adverso frecuente tras cirugía, con consecuencias clínicas y financieras significativas. Este artículo revisa las recomendaciones actuales basadas en evidencia para su manejo incluyendo aspectos claves en el manejo: la evaluación de factores de riesgo, tanto del paciente como relacionados con la anestesia y el tipo de procedimiento, se abordan medidas generales como rehidratación, preferencia por anestesia regional, evitar halogenados y reducir opioides. Destaca el uso de diversas opciones farmacológicas, incluyendo antagonistas de los receptores 5HT-3, inhibidores de los receptores NK-1, corticoesteroides, antidopaminérgicos, antihistamínicos, dexmedetomidina, propofol, mirtazapina y lidocaína, Se detallan los fármacos más relevantes, destacando su eficacia y perfiles de seguridad. Además, se exploran estrategias combinadas y terapias multimodales. Se examinan enfoques no farmacológicos como acupuntura, subrayando su aplicación preoperatoria y su relevancia en la medicina tradicional. Se proporciona orientación para abordar situaciones donde la profilaxis no logra prevenir la NVPO, destacando la importancia de combinaciones de

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fármacos para mejorar la eficacia del tratamiento de rescate. El artículo concluye señalando la evolución hacia enfoques multimodales en el manejo de NVPO, resaltando la diversidad de medidas disponibles y la necesidad de investigaciones adicionales para determinar estrategias óptimas en contextos clínicos específicos.

Palabras clave: *Náusea. Vómito. Farmacología. Profilaxis. Manejo multimodal.*

Introduction

Post-operative nausea and vomiting (PONV) is currently one of the most common adverse events after surgery. It is an unpleasant experience for the patient with clinical repercussions such as incisional pain, hematoma formation, suture dehiscence, esophageal rupture, bilateral pneumothorax, and delayed discharge from post-anesthesia care units (PACU). This series of complications delays hospital discharge and has a financial impact on the health institution[1,2].

The optimal management of PONV is complex and involves a number of aspects relevant to the outcome, including: assessment of the patient's risk, implementation of perioperative risk reduction measures, choice among the wide variety of antiemetics with different pharmacokinetic profiles, efficacy, adverse effects, the patient's clinical context, and rescue therapeutic measures in case of failure of prophylaxis.

At the institutional level, the management of PONV is influenced by various factors such as drug availability and cost–benefit strategies[1].

There are international guidelines for the management of PONV, however, they are limited for specific population groups, do not integrate all aspects of PONV management in sufficient detail, or are not updated with the most recent scientific evidence[3-5].

The main objective of this review is to summarize the most current evidence-based recommendations on the management of PONV.

Risk factors

There are risk factors specific to the patient, dependent on the anesthetic technique and dependent on the type of procedure to be performed[6,7]. Among the patient related risk factors, we include: female sex, history of PONV in previous surgery, previous diagnosis of vertigo, non-smoking status, and age < 50 years.

The risk factors associated with the anesthetic technique are the use of general anesthesia, use of intra- and post-operative opioids, use of inhalational anesthetics, use of nitrous oxide, use of neostigmine (> 3 mg) for reversal of neuromuscular blockade, and prolonged anesthesia time[7]. Finally, there are the risk factors associated with surgical procedures, among them those associated with a higher incidence of PONV are laparoscopic procedures, cholecystectomy, gynecological procedures. middle ear surgery, and neurosurgical procedures[8].

For the pediatric population, the Eberhart classification has been classically used to detect risk factors for PONV in children, which are personal or family history of PONV, age > 3 years and up to puberty, surgical time > 30 min, and the type of surgery such as strabismus corrective procedures[2,4,9].

Risk stratification

Due to the importance and relevance in clinical practice, it is crucial to assess the risk of developing PONV in all patients undergoing surgery. In this context, the question arises as to which is the most effective scoring system. Although several systems have sought to simplify this assessment as much as possible, there is a general consensus among experts in favor of the indicators proposed by Apfel and Koivuranta for adults, as well as that of Eberhart for children[2,8,10,11].

This specific model was validated in a group of patients undergoing various surgical interventions with balanced inhalational anesthesia. From this clinical approach, four independent predictive risk factors were identified: female gender, non-smokers, history of PONV, and use of opioids in the post-operative period. According to this model, the baseline risk is set at 10%, the presence of one risk factor is associated with a 20% probability of PONV, and each additional risk factor increases the risk by 20%, leading to a total risk of 80% when all four factors are present.

The risk stratification of PONV is classified as:

- Low risk: 0-1 risk factors present
- Intermediate risk: 2-3 risk factors
- High risk: 4-5 risk factors, depending on the scale used.

Preventive initial management

- Rehydration: restoring blood volume in patients who have fasted for ⩾ 12 h is one of the most cost-effective measures. It is recommended to follow fasting guidelines that allow consumption of clear liquids up to 2 h before surgery to prevent dehydration and thus reduce the risk of PONV[3].

– The use of regional anesthesia is recommended
– Avoid halogenated drugs such as nitrous oxide
– Reduction in the use of opioids in the pre- and post-operative period
– Use prophylactic drugs for PONV.

Prophilactic management of PONV

5HT-3 antagonists

Ondansetron is the most widely used and studied 5HT-3 receptor antagonist and is currently considered the drug of choice for the management of PONV[3]. It can be used as monotherapy or in combination with other prophylactic drugs. Other drugs available for perioperative use within this group are Granisetron, Ramosetron, and Palonosetron.

Granisetron is a first-generation antagonist and has a similar efficacy to 8 mg of dexamethasone. In middle ear surgeries and laparoscopic cholecystectomy, granisetron was found to be more effective than ondansetron in reducing PONV in the first 24 h postoperatively[12,13].

Ramosetron is a second-generation antagonist, approved for the management of nausea and vomiting. The most effective dose for adults is 0.3 mg IV. Adverse effects include drowsiness, dizziness, muscle pain, sedation, and constipation. It is recommended to add ramoseron 0.3 mg to an infusion of PCA opioid with good effectiveness. For the management of PONV, ramosetron has the same effectiveness as 4 mg of ondansetron[14,15].

Palonosetron is a second-generation antagonist with a half-life of 40 h, allosteric binding with receptor internalization and inhibition by double mechanism, blocking 5-HT3 and neurokinin 1 receptors. It has been shown to be more effective than 8 mg of ondansetron, 8 mg of dexamethasone, and 1 mg of granisetron. Palonosetron has demonstrated a clinical effectiveness similar to 40 mg of Aprepitant[13,15].

The use of palonosetron in general anesthesia with sevoflurane and nitrous oxide reduced the incidence of PONV in a similar way to a total intravenous anesthesia technique. The dose of 0.075 mg should be administered before or at the beginning of surgery[16].

Neurokinin-1 (NK-1) receptor inhibition

Aprepitant is a competitive antagonist of NK-1 receptors which was initially approved for the treatment of chemotherapy-induced nausea and vomiting.

It is administered orally although there is also an intravenous presentation in the form of a pro-drug called fosaprepitant.

Aprepitant has a half-life of 9 to 13 h and its duration of effect has been shown to be as long as 40 h.

It has been shown that 40-125 mg of aprepitant has a significant decrease in vomiting in the first 48 h postoperatively when compared to placebo or other combinations of antiemetics (ondansetron + dexamethasone).

It is an attractive drug in patients undergoing outpatient surgery since its action time is prolonged and this would decrease the incidence of nausea and vomiting in the late post-operative period[17,18].

Corticosteroids

Dexamethasone, like other synthetic glucocorticoids such as methylprednisolone, is mainly used as anti-inflammatory agents; however, for more than 30 years, its effectiveness in preventing nausea and vomiting induced by chemotherapy has been reported[19]. Its effectiveness in the management of PONV was subsequently demonstrated. Glucocorticoids have been included in international guidelines on the management of nausea and vomiting in the context of cancer patients undergoing chemotherapy and in guidelines for outpatient surgery and for the treatment of PONV[3,20]. Within the evidence and recommendations of the guidelines, it is established that glucocorticoids are effective only as prophylaxis and not as a treatment for vomiting.

The molecular mechanisms involved in the antiemesis of dexamethasone are not yet clearly described; however, the following have been demonstrated: (1) anti-inflammatory effect, inhibiting the formation of cytokines involved in vomiting, (2) direct central action on the nucleus of the solitary tract, (3) interaction with the release of neurotransmitters such as serotonin, neurokinin 1, neurokinin 2, and modulation of protein receptors, (4) regulation of the hypothalamus-pituitary-adrenal axis, and (5) analgesic effect decreasing opioid consumption[21].

At present, a dose of 4 to 10 mg (0.1 mg/kg) is recommended after induction. An efficacy similar to that of 8 mg of ondansetron has been reported. In addition, it has been concluded that the use of a single dose of 8 mg of dexamethasone does not increase the risk of infections in the post-operative period, the risk of delayed wound healing, surgical wound infection, anastomotic leak, bleeding, clinically significant hyperglycemia or the possibility of cancer recurrence is ruled out. Other glucocorticoids such as methylprednisolone have been evaluated at doses of 40 to 125 mg with good effectiveness for the prevention of PONV. Other steroids such as betamethasone have been used however have little effect when compared to placebo[22].

Antidopaminergic agents

Droperidol is effective in PONV prophylaxis at doses ranging from 0.625 to 1.25 mg. It is recommended to be administered at the end of surgery to optimize its antiemetic efficacy in the post-operative period. Recently, droperidol has fallen into disuse in many countries following an Food and Drug Administration warning about sudden cardiac death when doses of 25 mg were used. It has been suggested that the antiemetic dose is safe and has only been associated with QT prolongation on the electrocardiogram. The appearance of adverse effects may be dose-dependent, so doses of 0.625 mg are recommended at the end of surgery[3,5,23].

Haloperidol has been shown to be effective in preventing nausea and vomiting after surgery, although there are few comparative data with 5-HT antagonists[3]. In a diverse surgical population, the effectiveness and adverse effects of prophylaxis with 1 mg haloperidol were found not to differ significantly from those obtained with 4 mg ondansetron[24].

Metoclopramide acts as a dopaminergic D2 antagonist and has also been shown to have an effect on 5HT3 receptors. It is indicated for PONV prophylaxis and is recommended to be administered 15 min before the end of surgery. Recommended doses range from 10 to 25 mg IV[25,26].

Antihistamines

Diphenhydramine or dimenhydrinate is safely used in the treatment of PONV. It has similar efficacy to 5-HT3 receptor antagonists, and its efficacy is presumably due to the high concentration of histamine and muscarinic cholinergic receptors in the vestibular system. Recommended doses range from 25 to 50 mg. These medications have shown efficacy in reducing the incidence of nausea and vomiting after surgery. However, it is important to note that although they are considered safe, their use may be associated with common side effects including blurred vision and xerostomia[3,27].

- Diphenhydramine: Diphenhydramine is a first-generation antihistamine that has been used to prevent PONV. However, its use may be limited due to its sedative side effects.
- Dimenhydrinate: Another first-generation antihistamine, dimenhydrinate, has also been used to treat nausea and vomiting, especially in the setting of dizziness and motion sickness. Like diphenhydramine, it may have sedative effects.
- Promethazine: A second-generation antihistamine with antiemetic properties. It may be useful in the treatment of PONV but may also have side effects such as sedation and should be used with caution.

Importantly, treatment strategies for PONV often involve multifaceted approaches, and the choice of a specific medication may depend on several factors, including the patient's clinical condition, concomitant medications, and individual preferences.

Dexmedetomidine

Dexmedetomidine is a highly selective adrenergic agonist with analgesic and sedative properties. When administered intravenously, dexmedetomidine has been shown to reduce the incidence of post-operative pain and perioperative opioid consumption. Xu et al. reported in a meta-analysis of 106 clinical trials that dexmedetomidine, regardless of the mode of administration, whether bolus alone or bolus + continuous infusion, significantly reduced the incidence of PONV in adults and children when compared to placebo, and dexmedetomidine administration decreased perioperative opioid consumption. The authors suggest titrating and dosing the bolus or infusions appropriately to reduce adverse effects such as bradycardia and hypotension, especially when loading doses or intravenous boluses are administered. These findings suggest that the use of perioperative dexmedetomidine is a significantly superior measure for the control of PONV[28].

The antiemetic effect of dexmedetomidine is not yet described with certainty but is attributed to direct effects on the parasympathetic nervous system, inhibition of the adrenergic effect, and decrease of circulating catecholamines. In addition, the administration of dexmedetomidine has an indirect effect on the consumption of perioperative opioids, which would reduce the risk and incidence of presenting PONV[29-31].

The clinical use of dexmedetomidine to prevent nausea and vomiting is still uncertain. The literature describes that the best protocol for use is to administer a loading dose of 0.3-0.5 mcg per kg in 10-20 min followed by an infusion. intravenous 0.1-0.5 mcg/kg/h.

Propofol

Propofol, in addition to its properties as a hypnotic, acts positively in the prevention of nausea and vomiting in the post-operative period. Propofol doses of 10-20 mg IV have been shown to be effective in the management of nausea and vomiting with an effect of up to 6 h;

however, there are reports of a transient relief of the antiemetic effect, so it has been described to start a low-dose propofol infusion seeking a plasma concentration of 0.3-0.4 ng/mL to maintain the antiemetic effect for a longer time in case of recurrence of symptoms[32,33].

When using these measures, the clinical variables of each patient such as age, hemodynamic status, among others, must be taken into consideration before starting them and assessing the risk benefit of using this type of management.

Mirtazapine

Mirtazapine is effective in the prophylaxis of PONV by antagonizing 5HT receptors (30 mg po associated with dexamethasone 8 mg IV). It reduces PONV overall compared with placebo. Evidence of reduction in pre-operative anxiety has been observed, although mirtazapine increases the risk of sedation 30 mg po associated with dexamethasone 8 mg IV[34].

Lidocaine

Several studies demonstrating the beneficial effects of intraoperative IV lidocaine infusion, analgesic, antihyperalgesic, and anti-inflammatory properties have been described. A recent meta-analysis published in Cochrane demonstrated that perioperative administration of lidocaine reduced the risk of nausea during the first 48 h postoperatively[14,15].

Other reports indicate that administering lidocaine as an intravenous infusion at a rate of 1-1.5 mg/kg/h during and after abdominal surgery has a positive impact on patient recovery and reduces the length of hospital stay. A decrease in the occurrence of post-operative ileus was also observed, as well as a reduction in the incidence of PONV[29].

Benzodiacepines

Benzodiazepines (BZD) are drugs that act at the gamma-aminobutyric acid type A receptor level in a subunit specific for BZD. These drugs are routinely administered in the perioperative period for their anxiolytic, sedative, and amnesic properties[35]. In the context of the oncology patient, BZDs are recommended to prevent nausea and vomiting induced by chemotherapy and to provide amnesia and anxiolysis[36]. However, despite the evidence regarding the benefit of using these drugs, they have not yet been formally incorporated into international guidelines for the prophylaxis of PONV due to concerns about possible adverse effects such as delirium, oversedation, and increased days of hospital stay as a result of oversedation.

A systematic review was recently published in which 950 original articles and more than 100 randomized controlled studies were reviewed, evaluating the use of BZD in a perioperative manner and their outcomes. This work concludes that there is evidence suggesting that the use of BZD preoperatively or even postoperatively at anxiolytic doses (0.15-0.3 mg/kg) decreases the incidence of PONV, in addition to the fact that there are few studies that show possible harm or adverse effects on the patient[37].

Non-pharmacologic management

Acupressure and acupuncture, practiced in traditional Chinese medicine for thousands of years, are based on the concept of vital energy flowing through precise channels called meridians to functional organs. One of the primary functions of P6 is to regulate stomach function to prevent adverse qi flow. The body is considered a system, and disruptions in this system cause imbalances, affecting homeostasis and generating symptoms of disease. To restore balance, specific points (acupuncture points) on the skin are stimulated, connecting the meridians to the major organs. The choice of these points depends on the clinical diagnosis and the patient's meridians. Stimulation of acupuncture points has shown benefits in controlling blood pressure, angina, pain, nausea, and vomiting. Although the mechanism is not fully understood, it is believed that stimulation of these points triggers the release of endorphins and serotonin. At present, there is no consensus on the necessary duration of acupuncture point stimulation to achieve effectiveness, although at least 30 min before surgery is suggested[38].

Combined therapy: multimodal prophylaxis

Given the involvement of various pathways and receptors, it could be logically inferred that the joint administration of antiemetic drugs with different mechanisms of action is more effective than the use of a single drug in preventing PONV. Among the most studied and validated combination therapies are droperidol plus dexamethasone, 5HT3 receptor antagonist plus dexamethasone and 5HT3 receptor antagonist plus droperidol with no significant differences observed when comparing them[3].

In contrast to the information available on the prevention of PONV, there is less data on the efficacy of antiemetic therapy in patients who have already developed

Table 1. Drugs indicated for the prophylaxis and treatment of PONV

Drug	Dose	Common adverse effects	Time of administration
5HT-3 antagonists			
Ondansetron	4-8 mg	Headache, fatigue, constipation and increased liver enzymes.	30 min before the end of surgery
Palonosetron	0.075-0.25 mg	QT prolongation.	Before or after induction of anesthesia
Neurokinin 1 inhibitors			
Aprepitant	40-125 mg	Headache, constipation, fatigue	1-2 h before surgery
Corticosteroids			
Dexamethasone	4-10 mg (0.1 mg/kg)	Increased blood glucose, hypo/hypertension	After induction of anesthesia
Methylprednisolone	40-125 mg		
D2 dopaminergic angatonists			
Haloperidol	1 mg	QT prolongation, extrapyramidal effects, sedations or hypotension	30 min before the end of surgery
Droperidol	0.625-1.25 mg		
Methoclopramide	10-25 mg	Sedation, hypotension	End of the surgery
Antihistamines			
Diphenhidramine	25-50 mg	25-50 mg blurred vision xerostomia drowsiness	End of the surgery
GABA agonists			
Propofol	15-20 mg	Phlebitis drowsiness, respiratory depression, hypotension	TIVA or rescue measure at PACU

PONV: post-operative nausea and vomiting; PACU: post-anesthesia care units; GABA: gamma-aminobutyric acid.

PONV. The choice of therapy is influenced by whether or not prophylaxis was previously administered and the type of drug used for such prophylaxis. In situations where ondansetron or dexamethasone was used as a preventive measure and PONV develops, further administration of the same substance is not advised if more than 6 h have elapsed in the case of ondansetron or more than 24 h in the case of dexamethasone since its first administration. The therapeutic options available after carrying out the recommended prophylaxis are limited and managing established episodes of PONV can be challenging. It is essential to rule out treatable causes of nausea and vomiting, such as arterial hypotension, hypovolemia, pain, or a post-operative decrease in peristalsis[2].

Failure in prophylaxis

When a patient presents PONV, either because adequate prophylaxis was not given or prophylactic therapy failed, it is mandatory to initiate rescue pharmacological treatment with certain considerations, for example, prescribing an antiemetic of the same pharmacological class does not confer therapeutic benefit compared to placebo. If at least 6 h have passed since the last dose of antiemetic, a second dose of 5HT-3 antagonist or prescribing a butyrophenone could be considered in case there are no available alternatives. In patients who did not receive intraoperative prophylactic therapy, 5HT-3 receptor antagonists remain the first-line pharmacological treatment to treat nausea and vomiting. Ondansetron 4 mg IV or PO, ramosetron 0.3 mg IV, granisetron 0.1 mg IV or haloperidol 300 mcg are recommended, all of these drugs being equally effective[13], however, using butyrophenones could cause drowsiness in the patient[23,25].

The use of 20 mg IV propofol boluses has been described as an antiemetic in the PACU, with promising results; however it is recommended to use it with caution in patients over 60 years of age.

At present, combinations of drugs from different classes are recommended since superiority in treatment has been demonstrated. For example, ondansetron + dexamethasone + droperidol is more effective than either drug alone. Also, the combination of midazolam at a dose of 30 mcg per kg + ondansetron is superior to ondansetron alone. To date, an optimal or recommended combination has not been established, therefore, it is left to the discretion of the clinician and the patient's context[2,3].

Conclusion

The management of PONV has changed in recent years from administering no or one prophylactic drug

in high-risk patients to administering a multimodal prophylaxis regimen as part of daily clinical practice.

We include a table with the dosage and mechanism of action of the most commonly used drugs (Table 1). The introduction of novel therapies will allow the creation of combinations of antiemetic or rescue therapies. In addition, there is emerging evidence of treatment and non-pharmacological measures for the control of PONV, measures which have similar efficacy to pharmacological measures. Today, more than ever, there is a wide variety of antiemetic measures for patients. The efficacy of the different combination therapies requires further study.

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